In the United States Court of Federal Claims

OFFICE OF SPECIAL MASTERS

Filed: November 13, 2015

* * * * * * * * * * * * * * * * * * * *	**PUBLISHED**
LAURA DAY, as parent and natural guardian of B.K.D.,	
Petitioner,	No. 12-630V
v.	Chief Special Master Dorsey
SECRETARY OF HEALTH AND HUMAN SERVICES,	Entitlement; FluMist; Influenza Vaccine; Gardasil; Human Papilloma Virus; ("HPV"); Neuromyelitis Optica ("NMO")
Respondent.	
* * * * * * * * * * * * * * * * * * * *	

Anne Carrion Toale, Maglio, Christopher & Toale, Sarasota, FL, for petitioner.
Gordon Elliot Shemin, U.S. Department of Justice, Washington, D.C., for respondent.

RULING ON ENTITLEMENT[1]

I. Introduction

On September 24, 2012, Laura Day ("petitioner") filed a petition for compensation under the National Vaccine Injury Compensation Program ("the Program"),[2] as the legal representative of her daughter, B.K.D, in which she alleged that the Gardasil ("HPV") and FluMist ("influenza") vaccinations B.K.D. received on September 28, 2011, caused her to develop

[1] Because this published ruling contains a reasoned explanation for the action this case, the undersigned intends to post this decision on the website of the United States Court of Federal Claims, in accordance with the E-Government Act of 2002 § 205, 44 U.S.C. § 3501 (2012). In accordance with the Vaccine Rules, each party has 14 days within which to request redaction "of any information furnished by that party: (1) that is a trade secret or commercial or financial in substance and is privileged or confidential; or (2) that includes medical files or similar files, the disclosure of which would constitute a clearly unwarranted invasion of privacy." Vaccine Rule 18(b). Further, consistent with the rule requirement, a motion for redaction must include a proposed redacted ruling. If, upon review, the undersigned agrees that the identified material fits within the requirements of that provision, such material will be deleted from public access.

[2] The Program comprises Part 2 of the National Childhood Vaccine Injury Act of 1986, 42 U.S.C. § 300aa.

multiple sclerosis ("MS"). Petition at 3, ¶11. Petitioner further alleged that the vaccinations "actually caused, or, alternatively, significantly aggravated" B.K.D.'s injuries. Id. After the filing of the petition, it was discovered that B.K.D. actually suffers from a rare autoimmune disorder known as neuromyelitis optica ("NMO") or Devic's Syndrome, rather than MS. See Petitioner's ("Pet'r's") Exhibit ("Ex.") 6 at 13.

Respondent recommended against awarding compensation, stating that petitioner had not presented adequate evidence that B.K.D.'s Gardasil and FluMist vaccinations caused her to suffer from NMO. See Respondent's Rule 4 Report ("Resp't's Report") at 11. An entitlement hearing was held on June 10-11, 2015, in Washington, D.C., during which the petitioner, B.K.D., and the parties' respective experts testified. The parties filed post-hearing briefs and the case is now ripe for adjudication.

II. Factual Background

a. Summary of Relevant Facts

B.K.D. was born on August 25, 1998, in Mooresville, Indiana. Pet'r's Ex. 1 at 1. As a young child, B.K.D. enjoyed relatively good health, although she suffered from occasional ear infections and colds. Pet'r's Ex. 14 at 15. B.K.D.'s previous medical history includes symptoms of juvenile arthritis at the age of three and breaking her right wrist and the pinky finger on her right hand, for which she had surgery on September 17, 2011. Pet'r's Ex. 3 at 4; Pet'r's Ex. 4 at 5. B.K.D. was an otherwise active, healthy child who enjoyed playing competitive year-round softball. She received a physical examination at a CVS Minute Clinic in Mooresville, Indiana, on August 2, 2011, where she was cleared for participation in her school's sports programs. Pet'r's Ex. 16 at 1. The CVS nurse practitioner reported that B.K.D. "does not present apparent contraindications (including cardiovascular, musculoskeletal, and neurological) to practice and participate in [sports]." Id.

On September 28, 2011, at the age of twelve, B.K.D. received a FluMist and a third Gardasil vaccination at the Morgan County Health Department.[3] Pet'r's Ex. 7 at 1. On October 4, 2011, she presented to the emergency room of St. Francis Mooresville Hospital ("St. Francis") with complaints of abdominal pain, back pain, and generalized aches since October 1, 2011. Pet'r's Ex. 2 at 176. B.K.D. also reported experiencing abdominal pain when urinating and said that she had not had a bowel movement in two days. Id. at 178. Dr. Godfrey, the treating physician, concluded that B.K.D. was constipated and sent her home with instructions to take Miralax. Id.

On October 31, 2011, B.K.D. again presented in the emergency room at St. Francis complaining of constant diarrhea and a twelve pound weight loss over the course of the last two

[3] BKD received the first two rounds of the Gardasil vaccine on January 5, 2011, and May 25, 2011, respectively. She reported no adverse symptoms after receiving either of them. Pet'r's Ex. 7 at 1.

weeks. Pet'r's Ex. 2 at 186. She also reported a sore neck, fever, and a rash that began on or around October 27, 2011, along with irregular pupils. Id. B.K.D. tested positive for strep throat, and an analysis of her cerebrospinal fluid showed elevated protein levels. Id. at 194-96. She received a shot of Rocephin for treatment of suspected bacterial meningitis and was sent to Riley Hospital for Children ("Riley Hospital") for further evaluation. Id. at 190. Upon examination at Riley Hospital, the treating physicians suspected that B.K.D. could have viral or bacterial meningitis[4] and also suspected possible Horner's syndrome.[5] Pet'r's Ex. 4 at 14, 91-92.

After B.K.D. began complaining of leg weakness and numbness that progressively worsened, she had an MRI of her brain and spine on November 2, 2011. Pet'r's Ex. 4 at 93; Pet'r's Ex. 4 at 347. The MRI of her spine revealed findings consistent with acute disseminated encephalomyelitis ("ADEM").[6] Pet'r's Ex. 21 at 11. The MRI of her spine also revealed hyperintensity, and the MRI of her brain showed multiple T2 and FLAIR hyperintensities, all of which are consistent with ADEM. Pet'r's Ex. 4 at 349-50. Dr. Meredith Golomb, one of B.K.D.'s physicians at Riley Hospital, noted that B.K.D. had recently received both the Gardasil and FluMist vaccinations and planned to investigate the incidence of HPV vaccine and ADEM. When discussing the possibility of one of the vaccines causing ADEM, Dr. Golomb noted, "Although I think [it] is unlikely, [I] would not be able to rule [it] out entirely." Pet'r's Ex. 4 at 114. After speaking with an ADEM expert, Dr. Golomb noted in the file that B.K.D. "[received] Gardasil and FluMist on a [Wednesday], [and] had onset of band-like back pain [Saturday;] [the] gap for vaccine response [is] generally [five to] 42 days."[7] Pet'r's Ex. 4 at 123.

B.K.D. continued to receive treatment for ADEM, including both intravenous and oral steroids and Neurontin, until she was discharged from Riley Hospital on November 9, 2011. She was immediately transferred to Inpatient Pediatric Rehabilitation Services. Pet'r's Ex. 4 at 5. After spending a week in rehabilitation, B.K.D. regained much of her strength and was able to walk short distances when using a cane. Id. Her back, shoulder, and leg pain was controlled with Neurontin, and she continued taking oral steroids on a slow taper. B.K.D. was discharged from the rehabilitation facility on November 16, 2011. Id. at 6.

---

[4] While the Riley Hospital physicians initially postulated that B.K.D. suffered from either viral or bacterial meningitis, this diagnosis was later revised to neuromyelitis optica ("NMO").

[5] Horner's Syndrome is characterized by "homolateral miosis, mild ptosis, and apparent enophthalmos with slight elevation of the lower [eye]lid." Robert Kliegman et al., Nelson Textbook of Pediatrics, 2155 (19th ed. 2011).

[6] ADEM is "characterized by perivascular lymphocyte and mononuclear cell infiltration and demyelination . . . . It is believed to be a manifestation of an autoimmune attack on the myelin of the central nervous system." Daniel Albert et al., Dorland's Illustrated Medical Dictionary, 613 (32nd ed. 2012) ("Dorland's").

[7] Although B.K.D.'s MRIs of the brain and spine initially revealed findings consistent with ADEM, the parties agree that B.K.D. did not suffer from ADEM and that her correct diagnosis is NMO. See Pet'r's Ex. 6 at 4-5; Tr. 51.

When B.K.D. stopped taking oral steroids on December 16, 2011, her symptoms quickly worsened. On December 28, 2011, B.K.D. reported pupil irregularity, unsteady gait, right leg weakness, and back pain. She was admitted to Riley Hospital for overnight observation and was administered oral steroids. MRIs of her brain and spine were taken on December 29, 2011. The MRI of B.K.D.'s spine showed "areas of cervicothoracic cord expansion and … improving scattered thoracic meningeal enhancement." Pet'r's Ex. 11 at 36. However, B.K.D. continued to experience trouble walking. Pet'r's Ex. 9 at 11.

On January 5, 2011, B.K.D. again presented to the emergency room at Riley Hospital complaining of a severe headache and reporting that both of her legs felt numb, weak, and tingl**y**. Pet'r's Ex. 9 at 11-12. She also experienced back pain and urinary retention. Id. The next day, B.K.D. had an MRI of her brain which showed that the previous lesions in her brain had resolved. Pet'r's Ex. 9 at 3. On a brain MRI limited by metallic artifact and motion, no intracranial abnormalities were seen. Pet'r's Ex. 9 at 228. However, there was slight interval increase of the cervicothoracic spinal cord edema and expansion with new syrinx formation at T2 and T3. Id. at 229. The radiologist noted differential considerations, including ADEM and transverse myelitis. Id. B.K.D. was discharged from Riley Hospital on January 12, 2012, and was admitted to the pediatric rehabilitation facility, where she received treatment for persistent right lower limb weakness until she returned home on January 18, 2012. Id. at 4.

B.K.D. continued to recover until June 12, 2012, when she was again admitted to the emergency room at Riley Hospital with complaints of left hand and arm tingling, left leg weakness, and trouble running. Pet'r's Ex. 6 at 11. She also reported one episode of blurred vision in her left eye. An MRI of the brain showed no definite intracranial abnormalities, but an MRI of the spine showed extensive abnormalities from the C3 to the T6 level. Id. B.K.D. also tested positive for the aquaporin-4 antibody ("NMO IgG positive"), which is definitive of patients with NMO. Id. at 13.

On July 10, 2012, B.K.D. followed up with Dr. David Mattson, a neurologist with expertise in the treatment of MS, at the MS Center of Indiana University. Dr. Mattson noted that B.K.D. had a long segment of spinal cord demyelination, which is another symptom consistent with a diagnosis of NMO. Dr. Mattson did not initially diagnose B.K.D. with NMO because she had not shown symptoms of optic neuritis, which is one of the disease's most prominent symptoms. Ex. 6 at 5. He recommended that B.K.D. begin using Rebif, which is commonly used to treat patients with MS, in order to facilitate long-term management of the disease. Id. However, a Mayo clinic neurologist observed that an NMO-IgG positive test was "highly associated" with NMO, and B.K.D. was invited to participate in a study at the Mayo Clinic. Pet'r's Ex. 20 at 298. When B.K.D. began having trouble walking and was admitted to Riley Hospital on October 9, 2012, the attending neurologist, Dr. Walsh, noted that B.K.D. suffered from NMO. Pet'r's Ex. 12 at 5.

B.K.D. has been receiving treatment at the MS Center of Indiana University. On November 12, 2012, Dr. Mattson reaffirmed a decision to continue treating B.K.D. long-term with Rebif. Pet'r's Ex. 20 at 274. Rebif prevented B.K.D. from relapsing from the end of 2012 up until December 2013, when another relapse began. Tr. 18-19. On December 4, 2013, an MRI of her brain and spine showed new lesions, and B.K.D. began another round of steroids.

Pet'r's Ex. 35 at 5-6; Pet'r's Ex. 36 at 6. B.K.D. continued her visits to the MS Clinic, where her lower extremity symptoms continued and she was slowly weaned off steroids. After B.K.D. was seen at the MS Clinic on February 4, 2014, Dr. Grimes decided to switch her medication from Rebif to azathioprine in hopes of decreasing the enhancing activity in her brain and spinal cord. Pet'r's Ex. 36 at 4; Pet'r's Ex. 35 at 19.

b. Summary of Petitioner's and B.K.D.'s Testimony

Both petitioner, Laura Day, and her daughter, B.K.D., testified during the hearing on June 10, 2015. Ms. Day testified that although her daughter has never been diagnosed with rheumatoid arthritis, B.K.D. experienced aching in her legs when she was about two years old. Tr. 7. However, B.K.D. did not experience further problems after she visited a chiropractor, and she never visited a rheumatologist or had bloodwork done. Id. Ms. Day further stated that prior to receiving the Gardasil and FluMist vaccinations on September 28, 2011, her daughter was a happy, healthy seventh grader who enjoyed playing volleyball and softball. Tr. 9. B.K.D. received straight A's, she was in the National Honor Society, and she was the recipient of her school's prestigious presidential award. Id. Prior to September 2011, with the exception of getting a sports physical and receiving treatment for a sports injury, B.K.D. had not needed to go to the doctor in nearly four years. Tr. 7.

Ms. Day also testified about the ways in which her daughter's illness has impacted their family. She stated that since B.K.D.'s initial onset of NMO in September 2011, she has had to watch her daughter relearn to walk five times. Tr. 15. Ms. Day presented a clear timeline of her daughter's illness, beginning with the onset of symptoms and including B.K.D.'s second relapse of NMO in March 2012 and her third relapse in June 2012. Tr. 17-18. Ms. Day reported that after B.K.D. was diagnosed with NMO and began taking Rebif in June 2012, she enjoyed 14 months of good health and started to return to a more normal life, until her daughter's fourth relapse in December 2013. Tr. 20-21. Ms. Day described 2014 as a year of "one relapse after another," during which B.K.D. was hospitalized over ten times. Tr. 21-22. Ms. Day stated that in October 2014, B.K.D. began seeing Dr. Weinshenker, an NMO specialist at the Mayo Clinic. While her health has improved with an increase in her steroid treatment and an experimental chemotherapy drug treatment, it is still unclear whether this course of treatment will prevent further relapses of NMO. Tr. 21, 33. Additionally, Ms. Day reported that the medications used to control B.K.D.'s NMO make it difficult for her to enjoy a normal life and have caused her to gain over 120 pounds. Tr. 26.

Despite the uncertain future of her daughter's health, Ms. Day testified that B.K.D. has tried to make the most of her situation and enjoy life. Ms. Day stated that she and B.K.D. attended a prom at Riley Hospital and that B.K.D. enjoyed her sixteenth birthday party in Riley Hospital's lobby. Tr. 23, 25. B.K.D. also received a wish from the Make-A-Wish Foundation, where she, her family, and a friend traveled to California for a sightseeing trip. Tr. 28. And B.K.D.'s brother and his baseball team named one of their tournaments after B.K.D. and donated the money they raised to help pay for her treatment. Tr. 24. The family is hopeful that Dr. Weinshenker's new therapies will help B.K.D. to resume a more normal life.

In addition to petitioner's testimony, B.K.D. also testified. She described how the medications she takes for NMO make her feel tired, cause bruising in her arms, and occasionally make her sick. Tr. 41. B.K.D. testified about the difficulties of being in and out of the hospital and having to go to rehabilitation therapy to relearn how to walk. Tr. 43-44. She stated that she has had to teach herself how to walk many times, and that she has a cane, a walker, multiple leg braces, a gait belt, and two wheelchairs. Id. B.K.D. stated that her favorite color is orange because this is the awareness color for MS, which was one of her initial diagnoses. Tr. 46. B.K.D. concluded her testimony by stating, "I want to go to college to be a neurologist who specializes in MS and NMO." Tr. 50.

c. Procedural History

Petitioner filed this case on September 24, 2012, alleging that B.K.D. suffered from MS as a result of receiving the Gardasil and FluMist vaccinations on September 28, 2011. Petition at 1, ¶¶ 8-9. Petitioner filed the first set of medical records on November 2, 2011. Respondent addressed petitioner's claims in a report filed pursuant to Vaccine Rule 4(c), wherein respondent argued that petitioner was not entitled to compensation under the Program. Resp't's Report at 2. Respondent also asserted that petitioner had not filed a complete set of medical records or any affidavits in support of her position. Id. Additional time was granted for the filing of medical records, and petitioner filed an affidavit on July 24, 2013.

The parties also filed expert reports in support of their respective positions. On January 24, 2014, petitioner filed an expert report from neurologist Dr. Carlo Tornatore, his *curriculum vitae*, and several articles referenced in his report. Pet'r's Ex. 21. Dr. Tornatore concluded, "[B.K.D.] developed an HPV-induced ADEM/NMO mediated by an autoantibody to aquaporin-4." Id. at 11. Thereafter, respondent filed an expert report from neurologist Dr. Thomas Leist. Resp't's Ex. A. The parties also filed a joint pre-hearing submission outlining the facts and issues that were and were not in dispute. Joint Pre-Hearing Submission, filed May 15, 2015.

As stipulated by the parties, there are no disputed facts in this case.[8] The parties agree that B.K.D. received the Gardasil and FluMist vaccinations on September 28, 2011. They also agree that B.K.D. previously received two Gardasil vaccinations on January 5, 2011, and May 25, 2011. Joint Pre-Hearing Submission at 1. The parties also agree that B.K.D. had a positive NMO-IgG antibody test. Id. The parties agree that B.K.D. currently suffers from NMO and that her symptoms in early October 2011 were the initial presentation of what would later be diagnosed as NMO. Id.; Tr. 51.

[8] Petitioner's expert, Dr. Carlo Tornatore, initially posited in his expert report that B.K.D.'s October 1 symptoms were the result of ADEM and that she later developed NMO. See Pet'r's Ex. 21 at 11-12. However, the parties reached an agreement wherein petitioner and respondent stipulated that B.K.D.'s initial symptoms in early October 2011 were properly classified as symptoms of NMO and not of ADEM. See Joint Pre-Hearing Submission, filed May 15, 2015; Tr. 51.

The parties agree that B.K.D.'s alleged injury is not set forth on the Vaccine Injury Table,[9] nor is there any dispute as to whether B.K.D. received these vaccines in the United States.[10] Id. Additionally, the parties do not contest that B.K.D. has suffered from the residual complications of NMO for more than six months since the administration of the Gardasil and FluMist vaccinations.[11]

d. Issue to be Decided

The sole issue to be decided is whether the Gardasil and FluMist vaccinations administered to B.K.D. on September 28, 2011, were the cause of her NMO. Joint Pre-Hearing Submission at 2.

e. Neuromyelitis Optica (NMO)

NMO is a demyelinating autoimmune disorder consisting of optic neuritis and transverse myelopathy.[12] Optic neuritis is an inflammation of the optic nerve that is caused by antibodies that attack the myelin sheath[13] surrounding the optic nerve. Optic neuritis can lead to partial or total loss of vision.[14] Transverse myelitis is an abrupt onset of inflammation of the spinal cord that can cause permanent motor dysfunction.[15] An astrocyte is a special kind of myelin-producing cell.[16] In patients with NMO, the immune system becomes confused and begins to attack the body's astrocytes rather than foreign pathogens. When the astrocytes are attacked, this causes swelling in the brain and spinal cord. Tr. 67.

[9] See 42 U.S.C. § 300aa-11(c)(1)(A).

[10] See 42 U.S.C. § 300aa-11(c)(1)(B).

[11] See 42 U.S.C. § 300aa-11(c)(1)(D)(i).

[12] Institute of Medicine ("IOM"), Adverse Effects of Vaccines: Evidence and Causality, 642 (Kathleen Stratton et al. eds., 2012) (internal citations removed).

[13] Myelin is a substance that coils to form the myelin sheath and acts as an electrical insulator. Dorland's at 1218.

[14] Id. at 643.

[15] Adverse Effects of Vaccines at 646.

[16] Astrocytes are specialized neurological cells found in the central nervous system that "play a role in myelin formation, transport material to neurons and [aid in the] maintenance of the ionic environment of neurons." Dorland's at 169, 1265.

The study of NMO has been greatly advanced by the Mayo Clinic's discovery of anti-immunoglobin G ("NMO-IgG") antibodies in 2006. NMO-IgG antibodies target aquaporin-4 ("AQP4"), a protein that is present in astrocytes which helps conduct water through the cell membrane.[17] AQP4 is mainly concentrated in the eyes, brain, and spinal cord. In NMO patients, instead of the immune system eliminating foreign pathogens, the immune cells become confused and NMO-IgG antibodies begin to target AQP4, which then causes destruction of myelin and subsequent brain and spinal cord inflammation. Tr. 67. Because the triggering event that causes the NMO-IgG antibodies to attack the self is unknown, NMO is currently classified as an idiopathic disorder. Tr. 189.

III. Discussion

The Vaccine Act established the Program to compensate vaccine-related injuries and deaths. 42 U.S.C. § 300aa-10(a). "Congress designed the Vaccine Program to supplement the state law civil tort system as a simple, fair and expeditious means for compensating vaccine-related injured persons. The program was established to award 'vaccine-injured persons quickly, easily, and with certainty and generosity.'" Rooks v. Sec'y of Health & Human Servs., 35 Fed. Cl. 1, 7 (1996) (quoting H.R. Rep. No. 908 at 3, reprinted in 1986 U.S.C.C.A.N. at 6287, 6344).

a. Standards for Adjudication

Petitioner's burden of proof is a preponderance of the evidence. 42 U.S.C. § 300aa-13(a)(1). The preponderance of the evidence standard, in turn, has been interpreted to mean that a fact is more likely than not. Moberly v. Sec'y of Health & Human Servs., 592 F.3d 1315, 1322 n. 2 (Fed. Cir. 2010). Proof of medical certainty is not required. Bunting v. Sec'y of Health & Human Servs., 931 F.2d 867, 873 (Fed. Cir. 1991). A petitioner who satisfies this burden is entitled to compensation unless the government can prove by a preponderance of the evidence that the vaccinee's injury is "due to factors unrelated to the administration of the vaccine." 42 U.S.C. § 300aa-13(a)(1)(B).

b. Elements of Petitioner's Claim

When a petitioner alleges that an injury listed on the Vaccine Injury Table ("the Table") occurs within the time frame set forth in the Table, then petitioner's vaccine claim is deemed a Table claim, and a presumption of vaccine causation attaches. See 42 U.S.C. § 300aa-14; see also 42 C.F.R. § 100.3. If, however, a petitioner alleges an injury that is not listed on the Table, (such as the injury alleged in this case) the vaccine claim is deemed a non-Table case, and there is no presumption of causation. Rather, petitioner must satisfy her burden of proof. See 42

[17] Dorland's at 122; see also Tr. 67 (referencing Pet'r's Ex. 30 at 2).

U.S.C. § 300aa-13(a)(1)(A). In so doing, petitioner must show that the vaccine was "not only a but-for cause of the injury but also a substantial factor in bringing about the injury." Moberly, 592 F.3d 1320, 1321 (Fed. Cir. 2010) (quoting Shyface v. Sec'y of Health & Human Servs., 165 F.3d 1344, 1352-53 (Fed. Cir. 1999)).

Because petitioner does not allege that B.K.D. suffered a Table injury, she must prove that either the Gardasil or FluMist vaccines that B.K.D. received caused her injury. To do so, she must establish, by preponderant evidence: (1) a medical theory causally connecting the vaccine and B.K.D.'s injury ("Althen Prong One"); (2) a logical sequence of cause and effect showing that the vaccine was the reason for her injury ("Althen Prong Two"); and (3) a showing of a proximate temporal relationship between the vaccination and her injury ("Althen Prong Three"). Althen v. Sec'y of Health & Human Servs., 418 F.3d 1274, 1278 (Fed. Cir. 2005); 42 U.S.C. § 300aa-13(a)(1) (requiring proof by a preponderance of the evidence).

In determining whether petitioner is entitled to compensation, the special master shall consider all material contained in the record, § 300aa-13(b)(1), including "any … conclusion, [or] medical judgment … which is contained in the record regarding … causation … of the petitioner's illness." § 300aa-13(b)(1)(A). Thus, the undersigned must weigh the submitted evidence and the testimony of the parties' offered experts and rule in petitioner's favor when the evidence weighs in her favor. Moberly, 592 F.3d at 1325-26 ("Finders of fact are entitled – indeed, expected – to make determinations as to the reliability of the evidence presented to them and, if appropriate, as to the credibility of the persons presenting that evidence"); Althen, 418 F.3d at 1280-81.

i. Althen Prong One: Medical Theory of Causation

Under Althen Prong One, petitioner must set forth a medical theory explaining how the received vaccine could have caused the sustained injury. Andreau v. Sec'y of Health & Human Servs., 569 F.3d 1367, 1375 (Fed. Cir. 2009). Under this prong, a petitioner must make a showing that the received vaccine "can" cause the alleged injury. Pafford v. Sec'y of Health & Human Servs., 451 F.3d 1352, 1355-56 (Fed. Cir. 2006).

Petitioner's theory of causation need not be medically or scientifically certain, Knudsen, 35 F.3d at 548-49, but it must be informed by "sound and reliable medical or scientific explanation." Id. at 548; see also Veryzer v. Sec'y of Health & Human Servs., 98 Fed. Cl. 214, 223 (2011) (noting that special masters are bound by both § 300aa-13(b)(1) and Vaccine Rule 8(b)(1) to consider only evidence that is both "relevant" and "reliable"). If petitioner relies upon a medical opinion to support her theory, the basis for the opinion and the reliability of that basis must be considered in the determination of how much weight to afford the offered opinion. See Broekelschen v. Sec'y of Health & Human Servs., 618 F.3d 1339, 1347 (Fed. Cir. 2010) ("The special master's decision often times is based on the credibility of the experts and the relative persuasiveness of their competing theories."); Perreira v. Sec'y of Health & Human Servs., 33 F.3d 1375, 1377 n.6 (Fed. Cir. 1994) ("An expert opinion is no better than the soundness of the reasons supporting it.") (citing Fehrs v. United States, 620 F.2d 255, 265 (Ct. Cl. 1980)).

As noted above, the sole issue to be decided in this case is whether the vaccinations that B.K.D. received caused the injuries she sustained. Petitioner must show by a preponderance of the evidence that the Gardasil and FluMist vaccinations caused B.K.D. to develop NMO.

1. Petitioner's Expert, Dr. Tornatore

Dr. Carlo Tornatore, a board certified neurologist at Georgetown University Medical Center, testified on behalf of petitioner. Dr. Tornatore received his M.D. from Georgetown University School of Medicine, and he completed his residency in the Department of Neurology at Georgetown University Hospital. Pet'r's Ex. 55 at 2. Dr. Tornatore also completed a Fellowship in Molecular Virology at the National Institutes of Health. Id. He currently serves as the Vice Chairman of the Department of Neurology, the Director of the Georgetown Multiple Sclerosis Clinic, the Neurology Residency Program Director, and the Director of Neurology Clerkship for third year medical students at Georgetown University Hospital. Id. at 3; 7. He has been nominated for over 20 teaching awards and serves as an ad hoc reviewer for several neurology and virology journals. Id. at 4-6.

Dr. Tornatore is a member of the American Neurologic Association and the American Academy of Neurology, and he has published articles, book chapters, and abstracts on a range of topics in neurology and virology in several reputable medical journals. Id. at 8-14. He sees patients with NMO at Georgetown Hospital's MS Clinic, which he has run for nearly 20 years. Tr. 63. Of the clinic's 3,000 patients, Dr. Tornatore assists in the treatment of patients with Multiple Sclerosis, Guillain-Barré Syndrome, transverse myelitis/ADEM, and NMO. Tr. 63-64.

During the hearing, Dr. Tornatore opined that he believed to a reasonable degree of medical certainty that "B.K.D.'s NMO was caused by a combination of the Gardasil and influenza vaccinations she received on September 28, 2011." Tr. 66. Dr. Tornatore proposed three possible theories, discussed in greater detail below, to explain how the vaccinations B.K.D. received could have caused her NMO. The first and petitioner's primary theory of causation proposed by Dr. Tornatore was that of molecular mimicry. Tr. 96-97; see also Pet'r's Ex. 21 at 11-12. Dr. Tornatore's second theory was that the viral pathogens from the vaccines B.K.D. received upset the balance of her immune system, ultimately leading to a breakdown in her tolerance of self-antigens. Tr. 102-03. For his third theory, Dr. Tornatore posited that the co-administration of the Gardasil and FluMist vaccinations could have caused a misdirected immune response. Pet'r's Ex. 21 at 13-14.

a. Primary Theory of Causation: Molecular Mimicry

Dr. Tornatore explained molecular mimicry as the immune system's inability to distinguish between pathogen-derived antigens and self-antigens found in the tissue of the nervous system. Tr. 96-97. If both foreign antigens and self-antigens found within the body

share the same epitopes,[18] the immune system is unable to identify differences in foreign pathogens and the self, so it begins to attack the self. Tr. 97; see also Pet'r's Ex. 24 at 11-12. The immune system's responsive attack can then lead to activation of self-reactive lymphocytes, which will be concentrated in the target organ – in B.K.D.'s case, the nervous system – and cause inflammation and swelling. Tr. 97 (explaining Pet'r's Ex. 24 at 12).

As previously mentioned above, NMO damages the astrocytes. Pet'r's Ex. 30 at 2. AQP4 has been identified as the protein present in astrocytes which is the target for specific NMO antibodies. Tr. 65, 67. NMO is most often diagnosed by testing a person's blood serum for the presence of AQP4 antibodies, known as NMO-IgG. Pet'r's Ex. 30 at 3. Generally, when antigens are released into the body through a vaccine, a person's immune system will direct antibodies to bind to those foreign antigens and destroy them. However, in patients with NMO, NMO-IgG antibodies are triggered to attack the AQP4 proteins, which in turn destroy the astrocytes and cause swelling in the nervous system.[19] Molecular mimicry has been linked to the development of NMO due to the similarity in epitopes of AQP4 water channels and antigens found in the HPV vaccine. Pet'r's Ex. 31 at 1.[20] Dr. Tornatore explained that because the epitopes in NMO-IgG and HPV antigens are so similar, in some cases, the immune system does not correctly distinguish between the two and thus attacks the AQP4 channels on astrocytes as well as the viral antigens. Pet'r's Ex. 21 at 12.

Dr. Tornatore cited several studies in support of his opinion that the Gardasil and FluMist vaccinations led to B.K.D.'s development of NMO via the phenomenon of molecular mimicry. Dr. Tornatore relies on a study done by Noorbakhsh et al.,[21] where researchers attempted to predict when molecular mimicry might occur by looking for similarity between epitopes of pathogens believed to cause ADEM. Pet'r's Ex. 24; Tr. 98. Specifically, the researchers found homology between myelin basic protein and the hepatitis B vaccine, indicating the potential for molecular mimicry to occur. Pet'r's Ex. 24 at 11-12. Dr. Tornatore noted that although the Noorbakhsh paper focuses primarily on the hepatitis B vaccine causing ADEM, rather than Gardasil and/or FluMist causing NMO, the paper can still be used as evidence that the mechanism of molecular mimicry is a "true phenomen[on]." Tr. 101. The authors further note that patients can develop ADEM/transverse myelitis, which is one of the clinical presentations of NMO, after a flu vaccination. See Pet'r's Ex. 24 at 6; Tr. 103. According to Dr. Tornatore, the fact that the Noorbakhsh study found that post-vaccinal ADEM could be caused by a variety of vaccinations, including influenza, rabies, rubella, and hepatitis B vaccines, demonstrates that

[18] An epitope is the specific piece of the antigen to which an antibody binds, known as an "antigenic determinant." Dorland's at 637.

[19] Nelson Textbook of Pediatrics at 2077; see also Tr. 67.

[20] "Homology" is a term used to describe the molecular similarity between self-antigens and foreign antigens. Two proteins that are made up of similar amino acids are said to be homologous. Tr. 99.

[21] Farshid Noorbakhsh et al., Acute Disseminated Encephalomyelitis: Clinical and Pathogenesis Features, 26 NEUROL. CLIN. 759 (2008) [Pet'r's Ex. 24].

"multiple different antigenic stimuli lead to the same clinical phenomenology of inflammation in the spinal cord." Tr. 105 (referencing Pet'r's Ex. 24 at 6). In other words, NMO could be caused by many different antigens, including those found in both the Gardasil and FluMist vaccines.

Dr. Tornatore also referenced an NMO-specific study done by Menge et al.[22] In the Menge article, the authors reported four cases of NMO following HPV vaccination based upon a review of the VAERS database[23] for the years 2006 to 2009. Given the fact that NMO is so rare (0.25 – 1/100,000), especially in adolescents, the authors concluded that the incidence of HPV vaccine associated NMO was "unexpected and may not simply reflect the natural disease prevalence." Pet'r's Ex. 31 at 1. Moreover, during the years studied, there were only eight total NMO cases reported. Two of these cases were associated with the hepatitis B vaccine, and the others followed the flu vaccine (1 case) and the DTP vaccines (1 case). Id. These findings suggested that the HPV vaccine "might be overrepresented" as it relates to this rare condition. Id. While the authors could not, however, confirm "humoral immunologic cross reactivity" to be the cause of NMO following HPV vaccination, they did note that theoretically, there were similar amino acid sequences between AQP4 and HPV types 6, 11, 16, and 18. Table 1 below sets forth the authors' findings as to homology.

Table 1 **Assessment of immunologic cross-reactivity between AQ4 and L1 capsid proteins of HPV[a]**

	AA begin													AA end	Score (bits)	Expect value	Identities	Positives	Gaps
HPVtype18	163			C	A	G	V	E	I	G	R	G		171	14.2	8.2	5/9	5/9	0/9
				b		b			b	b		b							
AQP4	123			C	L	G	A	I	I	G	A	G		131					
				b	c	b			c	b		b							
HPVtype16	128			C	V	G	V	E	V	G	R	G		136	14.6	6.9	4/9	6/9	0/9
AQP4	158	H	G	L	L	V	E	L	I	I	T	F	Q	L	170				
		b	b				c	b				b	b	b					
HPVtype16	392	H	G	E	E	Y	D	L	Q	F	I	F	Q	L	404	15.4	3.4	6/13	7/13	0/13

[22] Til Menge et al., Neuromyelitis Optica Following Human Papillomavirus Vaccination, 79 NEUROLOGY 285 (2012) [Pet'r's Ex. 31].

[23] The Vaccine Adverse Event Report System (VAERS) database is a self-reporting system that tracks adverse events and/or side effects resulting from vaccinations. The program is jointly managed by the Centers for Disease Control and Prevention and the Food and Drug Administration. Adverse Effects of Vaccines: Evidence and Causality, 646 (Kathleen Stratton et al. eds., 2012).

Pet'r's Ex. 31 at 2.

In summary, the Menge authors posit that the theory of humoral immunologic cross reactivity (molecular mimicry) may be the medical theory of causation of NMO following HPV vaccine. In the alternative, they suggest "induction of bystander lymphocyte activation by upregulating both the adaptive and innate immune system." Pet'r's Ex. 31 at 2. Moreover, since L1 capsid proteins[24] of HPV and AQP4 share some similarities, Dr. Tornatore explained why everyone who is vaccinated for HPV does not develop NMO. Dr. Tornatore testified that the sequence homology between L1 and AQP4 is limited. He opined:

> [I]f someone were to be vaccinated with Gardasil and they happened to develop antibodies against these little stretches [of L1], those antibodies could then attach to aquaporin-4 and cause NMO. Is it possible that you could be vaccinated and have antibodies to L1, but that those antibodies are not directed against these little fragments? Of course. And then you'll never develop NMO … [S]ome people … [only] develop immunity to different parts of the L1 molecule … that [will] never … cross-react with aquaporin-4.

Tr. 112. Thus, as Dr. Tornatore explained, molecular mimicry can explain the development of NMO after a vaccine, but because the homology between the L1 protein and the AQP4 is limited, such an occurrence is extremely rare. Pet'r's Ex. 31 at 1-2.

Dr. Tornatore also cited several other studies which support his theory that the Gardasil and FluMist vaccinations can cause or contribute to the development of NMO. In a study by Karussis and Petrou,[25] the authors reviewed medical literature from 1979 – 2013 and assessed the incidence of central nervous system ("CNS") demyelinating diseases after vaccination. Pet'r's Ex. 42 at 1. They found a rather high proportion of "NMO-like disease" associated with influenza and HPV vaccination. Pet'r's Ex. 42 at 1. While the study found that the overall risk of contracting a demyelinating disorder such as NMO after a vaccination was "relatively low," the authors noted that in "a very high proportion of the patients (and especially following influenza vaccination) the dominant localizations of demyelination were the optic nerves and the myelin, presenting as optic neuritis and myelitis. This predisposition to the spinal cord and the optic nerves is reminiscent to … the NMO-spectrum of diseases" that are highly associated with anti-aquaporin-4 antibodies. Id. at 2 (emphasis added). The authors further reported that seven patients developed NMO-like disorders subsequent to Gardasil vaccinations, raising the possibility of cross-reactivity between AQP4 and viral proteins. Id.

[24] A capsid protein is the protein shell that typically encloses the genetic material of a virus. Dorland's at 284.

[25] Dimitrios Karussis & Panayiota Petrou, The Spectrum of Post-Vaccination Inflammatory CNS Demyelinating Syndromes, 13 AUTOIMMUN. REV. 215 (2014) [Pet'r's Ex. 42].

Dr. Tornatore also cited to a study by Fujinami and Oldstone[26] which addressed whether the sequence similarity between the L1 protein in HPV and AQP4 is sufficient to induce cross-reactivity. After looking at several demyelinating disorders, the study concluded that homology with as few as six amino acids is sufficient to induce cross-reactivity. Pet'r's Ex. 28 at 3-4. The authors stated, "Other investigators … have also shown that antibodies recognize as few as six amino acids." Pet'r's Ex. 28 at 4. Dr. Tornatore pointed out that the study shows that the immune system may be triggered based on homologies from very small amino acid residues, in rare cases, to cause NMO. Tr. 124.

In a study by Souyah et al.,[27] Dr. Tornatore opined that the HPV vaccine causes a "forty-fold increase in HPV antibodies" as compared to the antibodies created due to a "natural HPV infection." Pet'r's Ex. 48 at 3; Tr. 120. This fact, combined with a "genetic predisposition … to develop vaccine-induced autoimmunity," could explain why the HPV vaccine may play a role in causing injury via the mechanism of molecular mimicry or "other immune system stimulation mechanisms." Pet'r's Ex 48 at 3.

At the conclusion of his testimony during the hearing, Dr. Tornatore also referenced a study by Gautam et al.[28] The authors injected mice with a viral peptide with homology to myelin basic protein 1-11, which caused the development of experimental autoimmune encephalomyelitis (EAE). Pet'r's Ex. 40 at 2. The researchers showed that a sequence of only five peptide residues was sufficient to induce an autoimmune response leading to the development of EAE. The authors note, "Since only five native residues in a peptide are sufficient to induce EAE, it is conceivable that a pathogen with homology to self proteins at only a few residues may trigger autoimmune disease." Pet'r's Ex. 40 at 3. Dr. Tornatore urged, "This is very, very important and shows that [] very limited homology with very few amino acids can … cause an autoimmune response, [or] molecular mimicry." Tr. 125.

b. Dr. Tornatore's Other Theories

i. Immune System Imbalance

Although Dr. Tornatore's primary theory for how B.K.D. developed NMO from the Gardasil and FluMist vaccines is molecular mimicry, Dr. Tornatore also proposed two other

[26] Robert Fujinami & Michael Oldstone, Amino Acid Homology Between the Encephalitogenic Site of Myelin Basic Protein and Virus: Mechanism for Autoimmunity, 230 SCIENCE 1043 (1985) [Pet'r's Ex. 28]

[27] Nizar Souyah et al., Guillain-Barre Syndrome After Gardasil Vaccination: Data from Vaccine Adverse Event Reporting System 2006-2009, 29 VACCINE 886 (2011) [Pet'r's Ex. 48].

[28] Gautam et al., A Viral Peptide with Limited Homology to a Self Peptide Can Induce Clinical Signs of Experimental Autoimmune Encephalomyelitis, 161 J. IMMUNOL. 60 (1998) [Pet'r's Ex. 40].

theories of causation. The first alternative theory proposed by Dr. Tornatore is that of immune system imbalance. Dr. Tornatore referenced the Noorbakhsh report for the principle that viral pathogens can disturb the balance of the immune system causing an autoimmune disorder such as NMO. The Noorbakhsh researchers note:

> Even in the absence of epitopes common with self-antigens [i.e. homology leading to molecular mimicry], pathogens can cause autoimmunity by perturbing the intrinsic balance of the immune system, the so-called 'immunoregulatory mechanisms.' This could take place in the peripheral immune system, leading to a breakdown in the so-called 'self-tolerance' to self-antigens.

Pet'r's Ex. 24 at 12.

The Menge paper's authors also posit a mechanism whereby a disturbance of the balance of the immune system could lead to the development of a disorder such as NMO. The authors reported, "An alternative pathogenic concept [in the development of NMO] may be induction of bystander lymphocyte activation by upregulating both the adaptive and innate immune systems as was shown for HPV vaccines." Pet'r's Ex. 31 at 2. The authors suggest that a protein found in a vaccine could disrupt the immune system, causing it to lose its inhibitory properties and ultimately result in the development of an autoimmune disorder. Id.

ii. Misdirected Immune Response

With respect to the second alternative theory of causation, Dr. Tornatore briefly explained that concurrent administration of the Gardasil and FluMist vaccinations could have caused a misdirected immune system response. In reference to such an immune response, Dr. Tornatore stated:

> There is precedent for this in the animal model experimental [autoimmune] encephalomyelitis. In that model, animals are vaccinated with myelin basic protein mixed in an adjuvant … made to augment the immune response. Four days following dual vaccination, one would reasonably expect that there would be circulating activated lymphocytes that could then cross the blood-brain barrier and result in autoimmune inflammation. Indeed, a routine test for tuberculosis … is a common example of this type of phenomen[on].

Pet'r's Ex. 21 at 14.

2. Respondent's Expert, Dr. Leist

Dr. Leist is a professor of Neurology at Thomas Jefferson University and serves as the Chief of the Clinical Neuroimmunology Division and the Director of the Comprehensive Multiple Sclerosis Center at Thomas Jefferson University Hospital. Resp't's Ex. B at 1. Dr.

Leist also works as a neurology consultant at the Inglis Foundation and is the Director of the Hospital-based Neurology Infusion Service. Id. He graduated with a Ph.D. in biochemistry from the University of Zurich in Zurich, Switzerland, and he completed an M.D. at the University of Miami in Miami, Florida. Id. Dr. Leist is certified by the American Board of Psychiatry and Neurology, and he is a member of the American Medical Association, the American Academy of Neurology, the Society for Neuroimmunology, and the Society for Neurovirology. Id. at 1-2. Additionally, he has served as an advisor to the Vaccine Injury and Compensation Program for over ten years. Dr. Leist has written numerous peer-reviewed articles, book chapters, and abstracts on different facets of MS, and he has been invited to give lectures about the development of MS research around the world. Id. at 2-10. Dr. Leist has participated in a number of clinical trials on MS and optic neuritis. Id. at 10-11.

Dr. Leist opined that petitioner had not met her burden of presenting a preponderant medical theory causally connecting the Gardasil and FluMist vaccinations that B.K.D. received with her onset of NMO. Resp't's Ex. A at 1. Dr. Leist first testified that while molecular mimicry is a real phenomenon, it could not have led to B.K.D.'s development of NMO. Dr. Leist also testified that the co-administration of the third round of Gardasil and the FluMist vaccine could not have had any impact on the development of NMO.

a. Arguments Against Molecular Mimicry

Dr. Leist agreed that sequence homologies as described by Dr. Tornatore can be frequently found. Resp't's Ex. A at 10; Tr. 185. Dr. Leist introduced a paper by Albert and Inman[29] to demonstrate the frequency of sequence homologies. Resp't's Ex. C at 2-3; Tr. 179. The authors explain:

> The development of peptide-sequence data bases has resulted in the identification of many linear sequences of amino acids shared by organisms and humans, but many of these sequences lack any clinical correlation. Furthermore, it has been calculated that, on the basis of chance alone, up to 10 perfect matches can be found in protein-sequence data bases for a sequence of [five] amino acids.

Resp't's Ex. C at 2-3. However, Dr. Leist disagreed as to the significance of sequence homologies. Citing the Kohm[30] and Albert and Inman articles, Dr. Leist argued that if the "short-sequence homologies alone [were] sufficient to cause autoimmune disease, then [the] diseases [would] be very [] frequent." Tr. 180. Specifically with respect to petitioner's theory of causation, Dr. Leist testified that "showing a sequence homology or

[29] Lori Albert & Robert Inman, Molecular Mimicry and Autoimmunity, 341 NEW ENG. J. MED. 2068 (1999) [Resp't's Ex. C].

[30] Adam Kohm et al., Mimicking the Way to Autoimmunity: An Evolving Theory of Sequence and Structural Homology, 11 TRENDS IN MICROBIOLOGY 101 (2003) [Pet'r's Ex. 43].

… conformational homology between one protein and another protein alone is not sufficient to … prove that this is now causing an autoimmune disease." Tr. 180-81.

Turning to petitioner's medical literature in support of molecular mimicry, Dr. Leist pointed out that the Menge study did not confirm cross reactivity on the basis of serologic testing in patients with NMO. See Tr. 182; Pet'r's Ex. 31 at 1. Dr. Leist explained that the authors tested the capsid protein of HPV-1 to see whether it cross-reacted with AQP4 in patients with NMO, but the majority of patients did not have antibodies against the capsid proteins on HPV-1, meaning that the disorder was likely not the result of molecular mimicry in those patients. See Pet'r's Ex. 31 at 1-2; Tr. 182-83.

Moreover, Dr. Leist opined that the Menge study was not based on reliable data, as it was merely a collection of cases from the VAERS database. He argued, "[T]he Menge article is nothing but the collection of case reports" and thus its findings are not based on epidemiologic data." Tr. 214-15. In summary, Dr. Leist urged:

> [I]f we look at the sequence homology as discussed by Menge [] and view this in the context of the NMO situation … in my way of looking at this article, the sequence homology has been described, NMO has been observed, but the two events have not been linked beyond a temporal association.

Tr. 185.

Dr. Leist admitted, however, that the theory that NMO could be caused by molecular mimicry is not totally implausible. He testified, "[Molecular mimicry] could be a potential theory by which one could think … that [NMO] … could be caused. [But] sequence homology, in itself, is only one of the building blocks by which ultimately the molecular mimicry would … generate the disease." Tr. 204. Although Dr. Leist disagreed with Dr. Tornatore that molecular mimicry was the causal mechanism of B.K.D.'s development of NMO, he nonetheless acknowledged that molecular mimicry and sequence homology are real medical phenomena. Tr. 177.

Dr. Leist also referenced findings from the Institute of Medicine's Committee to Review Adverse Effects of Vaccines[31] ("IOM") to support his position that B.K.D.'s NMO was not caused by either the Gardasil or the FluMist vaccine. The IOM reported, "No studies were identified in the literature for the Committee to evaluate the risk of neuromyelitis optica (NMO) after the administration of HPV vaccine . . . . The epidemiological evidence is insufficient or absent to assess an association between HPV vaccine and NMO." Resp't's Ex. I at 6. Dr. Leist opined that NMO is not caused by the HPV vaccine, as the IOM was unable to find an association between the two. Resp't's Ex. I at 6.

[31] Kathleen Stratton, "Evaluating Biological Mechanisms of Adverse Events," *in* Institute of Medicine, Adverse Effects of Vaccines: Evidence and Causality 51 (Stratton et al., eds. 2011) [Resp't's Ex. I].

Furthermore, Dr. Leist disputed the relevance of the medical literature on which Dr. Tornatore relied to support his opinions. See Resp't's Ex. A at 10 (referencing Pet'r's Exs. 21, 23, 25 and 32). Dr. Leist's expert report references studies by Tenembaum et al.[32] and Johnson,[33] which petitioner offered to show that the development of ADEM can follow a vaccination. See Pet'r's Ex. 21 at 11-12; Pet'r's Ex. 25 at 1; Pet'r's Ex. 23 at 1. Dr. Leist stated that B.K.D. never suffered from ADEM and thus, the Tenembaum and Johnson studies were irrelevant in B.K.D.'s case.[34] He stated, "I think that the Tenembaum report does not really provide evidence of association with a particular infection or infections and ADEM beyond temporality." Tr. 189-90.

Dr. Leist also opined that Dr. Tornatore's reference to the Schonberger et al. study[35] showing that GBS is often preceded by an influenza vaccination was also irrelevant, as B.K.D. was never diagnosed with GBS. Resp't's Ex. A at 10; (referencing Pet'r's Ex. 32 at 1). However, Dr. Tornatore's references to the Tenembaum, Johnson, and Schonberger studies were not determinative of the outcome in this case, nor were they central to the petitioner's causal theory, and thus the undersigned does not find Dr. Leist's argument persuasive on this point.

b. Arguments Against Petitioner's Alternative Theories

With respect to Dr. Tornatore's theory that the Gardasil and FluMist vaccinations caused an imbalance of B.K.D.'s immune system, Dr. Leist stated that the Noorbakhsh study which Dr. Tornatore referenced in support of this second theory was not applicable to B.K.D.'s situation because it focused on ADEM, rather than NMO. Resp't's Ex. A at 10. Specifically with respect to the Noorbakhsh study, Dr. Leist opined, "It is my opinion that [B.K.D.] did not suffer from ADEM … [This article] is therefore not related to this case." Id.

Dr. Leist's also addressed Dr. Tornatore's third causative theory regarding the co-administration of the Gardasil and FluMist vaccinations causing B.K.D. to experience a

---

[32] Silvia Tenembaum et al., Acute Disseminated Encephalomyelitis: A Long-Term Follow-Up Study of 84 Pediatric Patients, 59 NEUROLOGY 1224 (2002) [Pet'r's Ex. 25].

[33] Richard Johnson, The Pathogenesis of Acute Viral Encephalitis and Postinfectious Encephalomyelitis, 155 J. INFECTIOUS DISEASES 359 (1987) [Pet'r's Ex. 23].

[34] As B.K.D. was initially diagnosed with ADEM, the parties initially disputed whether B.K.D. suffered from ADEM prior to her onset of NMO. See Pet'r's Ex. 4 at 7. However, the parties later agreed that B.K.D.'s correct initial diagnosis was NMO or an NMO spectrum disorder and that she never suffered from ADEM. Tr. 51.

[35] Lawrence Schonberger et al., Guillain-Barre Syndrome Following Vaccination in the National Influenza Immunization Program, United States, 1976-1977 110 AM. J. EPIDEMIOLOGY 105 (1979) [Pet'r's Ex. 32].

misdirected immune response. See Resp't's Ex. A at 11. Dr. Leist referenced a study by Martinón-Torres et al.,[36] which analyzed various safety concerns associated with the co-administration of pediatric vaccinations and found a "favorable safety profile in both infants and toddlers." Resp't's Ex. F at 7. However, the study did not provide any information on the Gardasil or FluMist vaccines. Dr. Leist stated, "While HPV was not included in the [Martinón-Torres] study, the authors did not report occurrence of unexpected side effects resulting from multiple vaccine administrations at a time." Resp't's Ex. A at 11.

3. Evaluation of the Evidence

The undersigned evaluates the parties' respective experts' opinions based on the record as a whole. Snyder v. Sec'y of Health & Human Servs., 88 Fed. Cl. 706, 742-43 (Fed. Cl. 2009) (citing General Electric Co. v. Joiner, 522 U.S. 136, 146 (1997)).

The undersigned finds that there is preponderant evidence in the record to demonstrate that the Gardasil and FluMist vaccinations led to B.K.D.'s development of NMO through the mechanism of molecular mimicry. In support of his theory, Dr. Tornatore used the Menge study to show that there is sequence homology between HPV types 16 and 18 and AQP4. Pet'r's Ex. 31 at 2 (referencing Table 1); Tr. 111. This sequence homology demonstrates the potential for cross-reactivity to occur. Pet'r's Ex. 31 at 2.

Dr. Leist testified that if frequently occurring short sequence homologies were sufficient to induce an autoimmune reaction, then there would be a high incidence of autoimmune disorders in the general population. Tr. 180. However, Dr. Leist did not address Dr. Tornatore's explanation of why people only rarely develop autoimmune disorders due to sequence homology that then results in molecular mimicry. According to Dr. Tornatore, "[It is] possible that [a person] could be vaccinated and have antibodies to L1 but [that] those antibodies are not directed against these little fragments [on the HPV antigen] … Some people are going to develop immunity to different parts of the L1 molecule … that [will] never … cross-react with aquaporin-4." Tr. 112.

In addition to his opinion that the sequence similarity between L1 and AQP4 was sufficient to induce cross-reactivity and cause B.K.D. to develop NMO, Dr. Tornatore cited studies by Karussis and Petrou, Gautam, and Fujinami & Oldstone demonstrating that the sequence similarity between L1 and AQP4 is sufficient to induce cross reactivity. Pet'r's Ex. 42 at 2 (assessing the incidence of NMO after HPV vaccination and concluding that there was a possibility of cross-reactivity between L1 and AQP4); Pet'r's Ex. 40 at 3 (finding that "it is conceivable that a pathogen with homology to self proteins at only a few residues may trigger autoimmune disease"); Pet'r's Ex. 28 at 3-4 (addressing whether the sequence similarity is sufficient to induce cross-reactivity between L1 and AQP4); Tr. 116.

[36] Federico Martinón-Torres et al., 13-Valent Pneumococcal Conjugate Vaccine Given with Meningococcal C-Tetanus Toxoid Conjugate and Other Routine Pediatric Vaccinations: Immunogenicity and Safety, 31 PEDIATRIC INFECTIOUS DISEASE J. 392 (2012) [Resp't's Ex. F].

Therefore, the undersigned finds that petitioner has provided preponderant evidence that the Gardasil and FluMist vaccinations can cause NMO via molecular mimicry. Accordingly, petitioner has satisfied Althen Prong One.

ii. Althen Prong Two: Logical Sequence of Cause and Effect

Under Althen Prong Two, petitioner must prove "a logical sequence of cause and effect showing that the vaccination was the reason for [B.K.D.'s] injury." Althen, 418 F.3d at 1278. This requires petitioner to show by preponderant evidence that the vaccines B.K.D. received actually caused the alleged injury. Pafford, 451 F.3d at 1354. Petitioner need not make a specific type of evidentiary showing. That is, petitioner is not required to offer "epidemiologic studies, re-challenge, the presence of pathological markers or genetic disposition, or general acceptance in the scientific or medical communities to establish a logical sequence of cause and effect." Capizzano v. Sec'y of Health & Human Servs., 440 F.3d 1317, 1325 (Fed. Cir. 2006). Instead, petitioner may satisfy her burden by presenting circumstantial evidence and reliable medical opinions. See id. at 1325-26.

1. Petitioner's Expert, Dr. Tornatore

a. Logical Sequence of Cause and Effect

Dr. Tornatore opines that there is a logical sequence of cause and effect between the Gardasil and FluMist vaccinations B.K.D. received and her subsequent development of NMO. Pet'r's Ex. 21 at 10-11; Tr. 127-30. Dr. Tornatore discussed the onset of B.K.D.'s NMO in three phases. In phase one, B.K.D. received two previous Gardasil vaccinations in January and May 2011. Dr. Tornatore explained that B.K.D.'s immune system would have responded to the antigens found in these first two Gardasil vaccinations. Pet'r's Ex. 21 at 11. However, Dr. Tornatore clarified that these first two Gardasil vaccinations did not lead to the development of NMO because the antibody titers that developed as a result of the vaccine were too low and thus the immune response was not sufficient to lead to the onset of NMO symptoms. Tr. 128.

After B.K.D. received the third Gardasil vaccination on September 28, 2011, Dr. Tornatore explained that her immune system developed an immediate response to the HPV antigens. During this immune response, autoimmune antibodies were directed to the L1 protein found in the HPV vaccine, and those antibodies "very quickly [found] the homology in aquaporin-4 in the nervous system, and so those antibodies hone[d] in on that area, and then they start[ed] to cause inflammation … initially in the lower thoracic [area]." Tr. 128. The immune system's timely response to the HPV antigens thus resulted in B.K.D.'s initial symptom onset of abdominal pain on October 1, 2011. Tr. 128; Pet'r's Ex. 21 at 11.

In phase two of his causation theory, Dr. Tornatore detailed the progression of B.K.D.'s symptoms. Pet'r's Ex. 2 at 176. He explained that B.K.D.'s abdominal pain was caused by inflammation of her spinal cord. Pet'r's Ex. 21 at 11. Dr. Tornatore stated:

> The spinal cord inflammation was due to an immune response directed at antigens in the spinal cord with homology to the antigens found on the HPV vaccine (molecular mimicry). Indeed, [B.K.D.] had antibodies to aquaporin-4 antigens (NMO antibodies), [] which have homology with human papilloma virus … It is highly probable that the inflammatory lesions seen on the MRI of the brain may have occurred during this time frame as well, however, they were in non-eloquent areas of the brain and [did not cause symptoms].

Pet'r's Ex. 21 at 11. Dr. Tornatore's testimony connected B.K.D.'s NMO symptom onset approximately three days after receiving the Gardasil and FluMist vaccinations with the clinical symptoms of abdominal pain and generalized aches that she reported experiencing at that time.

In the third phase of his theory, Dr. Tornatore reported that three and a half weeks after receiving the vaccinations, B.K.D. developed inflammation in her spinal cord, which resulted in weakness in her lower extremities. Pet'r's Ex. 21 at 11. Dr. Tornatore opined that this acute inflammation is reflected in B.K.D.'s November 2, 2011 spinal MRI. See Pet'r's Ex. 4 at 93. Dr. Tornatore stated that the MRI of the spine shows that B.K.D.'s NMO could not have been caused by her strep infection[37] in late October 2011. He reported, "The previous areas of inflammation in the lower thoracic spine and brain did not enhance with gadolinium, consistent with inflammatory areas that were several weeks old, clearly preceding the strep infection that [B.K.D.] was diagnosed with on [October 31, 2011]." Pet'r's Ex. 21 at 11. According to Dr. Tornatore, the approximate onset of NMO can be deduced by reviewing B.K.D.'s MRIs of the brain and spine concurrently with her progression of symptoms. The MRI findings on November 2, 2011, conclusively demonstrate that the onset of NMO occurred around the first week of October, shortly after B.K.D. received the Gardasil and FluMist vaccinations. Tr. 128-29.

Although Dr. Tornatore spent a great deal of time during the hearing discussing how the Gardasil vaccination caused B.K.D.'s NMO, he also discussed how the FluMist vaccination could have created the immune response. Dr. Tornatore testified, "And the same thing … [goes for] the FluMist [vaccination] … the antigens on that virus may trigger the immune system, and that then causes the inflammation in the spinal cord, and then … [you] release antigens, you have epitope spreading,[38] [] you develop antibodies against aquaporin-4, and you may get the full-blown NMO developing." Tr. 132.

---

[37] Respondent's expert agrees that B.K.D.'s strep infection was not the cause of her NMO. Tr. 176-78.

[38] With regard to the phenomena of "epitope spreading", Dr. Tornatore analogized, "[I]f you have a cabinet and it catches fire, if you put it out very quickly, you'll only get a little char on the outside of the cabinet. If, on the other hand, the inflammation continues, the top of the cabinet may get burnt [sic] away, and now you can look inside, and you can see the utensils inside the drawer. So, those antigens that were hidden are now exposed, and then you could develop an immune response against that. And so that's what we call epitope spreading. The more the

b. B.K.D.'s Genetic Predisposition to Autoimmune Disorders

Dr. Tornatore also discussed how B.K.D.'s family history of autoimmunity may have predisposed her to develop an autoimmune disease from a vaccination. Tr. 131. The medical record documents that several of B.K.D.'s family members have suffered from autoimmune disorders. B.K.D.'s paternal grandmother suffered from rheumatoid arthritis and Graves' disease,[39] her father had Crohn's disease,[40] her brother currently suffers from a seizure disorder, and a paternal cousin has MS. Pet'r's Ex. 57 at 19; Pet'r's Ex. 3 at 4. Dr. Tornatore stated that a family history of autoimmunity suggests a genetic predisposition to the development of other autoimmune disorders. He testified, "Clearly, there are genes that are predisposing her family to autoimmunity, [so] that their immune system is more likely to attack self-antigens" than someone else's immune system. Tr. 130. He stated that the exact genetic process is unknown but that there are a few theories of how a person's genetic makeup can affect her autoimmunity. According to Dr. Tornatore:

> [S]omehow [a person's genes] either release[] the inhibition of … white blood cells so that they [are] not kept down or they may in some way play a role in activating one's immune system in the right type of antigen presentation. So, a family history of autoimmunity would suggest that [B.K.D.] was at risk for developing an autoimmune disease in the right setting.

Tr. 131.

Thus, Dr. Tornatore explained that because several other people in B.K.D.'s immediate family have experienced issues with autoimmune disorders, it is likely that B.K.D. would be more likely to develop an autoimmune disorder than the average person. In conclusion, Dr. Tornatore summarized, "[T]he … FluMist, in combination with the Gardasil, in the right timing, with the third dose of Gardasil, in the right person, with the right genetic background, [it] may have been [a] perfect storm that … then caused the NMO to develop." Tr. 130-31.

---

inflammation goes on, the more immunity you develop against many different things, because now they're exposed where they previously weren't." Tr. 132-33.

[39] Graves' disease is an autoimmune disorder that affects the thyroid. Although the exact cause of the disease is still unknown, disease onset is believed to be genetic. The disease occurs when antibodies cause the thyroid gland to produce excess hormones, causing hyperthyroidism. Robert Kliegman et al., Nelson Textbook of Pediatrics 1909-11 (19th ed. 2011).

[40] Crohn's disease is a chronic inflammation of the bowel caused by a combination of environmental, bacterial, and immune factors. Although Crohn's has not been classified as an autoimmune disorder, it is believed that the immune system directs itself against microbial antigens found in the gastrointestinal tract, thus resulting in inflammation. Nelson at 1300-03.

2. Respondent's Expert, Dr. Leist

While Dr. Leist agreed with Dr. Tornatore that B.K.D. suffers from NMO, he argued that NMO is an idiopathic disorder. See Tr. 187. He then turned to a discussion of B.K.D.'s potential genetic predisposition to autoimmune disorders, arguing that her genetic predisposition, rather than the Gardasil or FluMist vaccinations, led to her onset of NMO. Dr. Leist also stated that B.K.D.'s family history of autoimmune disorders and her juvenile arthritis,[41] which could have potentially been an early manifestation of an autoimmune disease, show that B.K.D. could have developed NMO due to a genetic predisposition toward autoimmune diseases and not because she received the Gardasil and FluMist vaccinations. Tr. 200.

Dr. Leist referenced a paper by McKeon et al.,[42] which studied serologic evidence from individuals with multiple autoimmune disorders. Resp't's Ex. G at 2. The study tested children whose sera were positive for the NMO-IgG antibody to determine whether coexisting auto-antibodies were also present. Out of 75 total children with NMO-IgG antibodies, 57 showed additional auto-antibodies and 16 out of 38 children had an additional, co-existing autoimmune disease, including juvenile rheumatoid arthritis and Grave's disease. Id. Dr. Leist pointed out that as a child, B.K.D. may have had symptoms consistent with juvenile rheumatoid arthritis, which is classified as an autoimmune condition. See Pet'r's Ex. 3 at 4; Tr. 200. Dr. Leist conceded, however, that his opinion in the case "is not dependent on the presence of another autoimmune disease." Tr. 200.

3. Evaluation of the Evidence

Dr. Tornatore's opinion regarding a logical sequence of cause and effect is pursuasive and is supported by B.K.D.'s medical records. Dr. Tornatore opined that the Gardasil and FluMist vaccinations B.K.D. received on September 28, 2011, initiated a brisk immune response to specific antigens found in the Gardasil vaccine through the process of molecular mimicry. Petr's Ex. 21 at 11. Dr. Tornatore noted, "[O]ne of the most interesting pieces of information regarding the timing of [B.K.D.'s] symptom onset is her MRIs of the brain and spine done November 2, 2011, which correlate precisely with her symptoms." Pet'r's Ex. 21 at 14. Dr. Tornatore opined that B.K.D.'s spinal MRI on November 2, 2011, showed an area of inflammation in the spinal cord from T9 to T12, consistent with B.K.D.'s complaints of "band-like" abdominal pain in early October. Pet'r's Ex. 21 at 14; Tr. 89. The inflammation of the thoracic spinal cord caused B.K.D.'s abdominal discomfort and the back pain. Tr. 94.

---

[41] Petitioner testified during the hearing that B.K.D. never suffered from juvenile rheumatoid arthritis. Tr. 7. Petitioner stated that when B.K.D. was two years old, she once complained of leg pain, but after she was evaluated by a chiropractor, B.K.D. never experienced further episodes. Id.

[42] A. McKeon et al., CNS Aquaporin-4 Autoimmunity in Children, 71 NEUROLOGY 94 (2008) [Resp't's Ex. G].

B.K.D.'s MRI of her spine on November 2, 2011, showed a relatively new inflammation of her upper cervical spine, which would explain why she began experiencing head and neck pain as well as leg weakness on October 31, 2011. Tr. 89-90; Pet'r's Ex. 2 at 190; Pet'r's Ex. 4 at 11, 13. Dr. Tornatore summarized, "[B.K.D.'s] MRI[s] [are] a beautiful, beautiful ability for us to look back in time" and see a clinical picture of the onset and progression of [B.K.D.'s] NMO after she received the Gardasil and FluMist vaccinations. Tr. 91.

Dr. Leist agreed with B.K.D.'s diagnosis of NMO, but he opined that the vaccinations she received on September 28, 2011, could not have caused the initial symptoms of NMO that she developed three days later. Resp't's Ex. A at 7-8. In refutation of Dr. Tornatore's theory of causation, Dr. Leist stated that the precise cause of NMO is unknown. Tr. 187. Dr. Leist suggested that BKD's NMO was an "underlying condition [that] was already ongoing …" and could have been due to a genetic predisposition to autoimmune disorders. Tr. 225; Resp't's Ex. A at 9-10. Dr. Leist did not refute the interpretation of B.K.D.'s MRIs by Dr. Tornatore. Instead, he focused on the fact that NMO is currently classified as an idiopathic disorder. Tr. 188-89. Dr. Leist also emphasized, "[B.K.D.] may carry a diagnosis of juvenile rheumatoid arthritis, an autoimmune condition." Resp't's Ex. A at 9.

Both experts agree that BKD may have been predisposed to developing autoimmune disease. Dr. Tornatore stated:

> [E]ssentially, if you have bad genes, then you[r] [body] [is] not going to be able to adequately control [an autoimmune] response, or if your genes are such that … there is an inherent genetic problem in your family, given the … right antigen in the right circumstance, you could then develop an autoimmune process. And … that's what we feel happened with B.K.D.

Tr. 230.

For all of the reasons stated above, the undersigned finds that petitioner has shown by preponderant evidence a logical sequence of cause and effect that B.K.D.'s HPV and flu vaccinations caused her to develop NMO. Thus petitioner has satisfied her burden under Althen Prong II.

iii. Althen Prong Three: Timing

Under Althen Prong Three, petitioner must establish that B.K.D.'s injury occurred within a time frame that is medically appropriate for the alleged mechanism of harm. See Pafford, 451 F.3d at 1358 ("Evidence demonstrating petitioner's injury occurred within a medically acceptable time frame bolsters a link between the injury alleged and the vaccination at issue under the 'but-for' prong of the causation analysis."). Petitioner may meet her burden by showing: (1) when the condition for which she seeks compensation first appeared after vaccination, and (2) that the period of symptom onset is "medically acceptable to infer causation." Shapiro v. Sec'y of Health & Human Servs., No. 99-552V, 2011 WL 1897650, at *13 (Fed. Cl. Spec. Mstr. Apr. 27, 2011), granting in part, vacating in part, 101 Fed. Cl. 532

(2011); aff'd, 503 F. App'x 952 (2013) (per curiam). The appropriate temporal association will vary according to the particular medical theory advanced in the case. See Pafford, 451 F.3d at 1358.

1. Petitioner's Expert, Dr. Tornatore

a. Sufficient Period of Time Between Vaccination and Onset of NMO

The medical records demonstrate that three days after B.K.D. received the Gardasil and FluMist vaccinations, she began experiencing symptoms consistent with the initial onset of NMO, including abdominal pain, lack of bowel movement, and generalized aches. Pet'r's Ex. 2 at 178.[43] Dr. Tornatore testified that the timing of B.K.D.'s third round of Gardasil and FluMist vaccinations on September 28, 2011, and B.K.D.'s initial symptoms on October 1, 2011, sufficiently demonstrates a proximate temporal relationship between the vaccinations and B.K.D.'s subsequent development of NMO. Dr. Tornatore cited medical literature to support his opinion that the time period between a vaccination and NMO symptom onset can be anywhere from two to 42 days. Tr. 138. He first referenced a report published by the IOM[44] discussing the latency period between antigen exposure and immune response. The report describes the latency period between vaccination and initial symptom presentation as the "lag phase." Pet'r's Ex. 47 at 1. The IOM report explains:

> The lag phase is characterized by the initial activation of B and T cells upon encounter with the antigen for which they are specific, and this triggers the cells' differentiation into effector and memory cells.[45] The lag phase between primary exposure to an antigen and the logarithmic phase is classically thought to be four to seven days, but it varies depending on route of exposure and the antigen itself.

Id. at 1.

Although the IOM study shows a lag phase beginning at four to 10 days, Dr. Tornatore stated that because B.K.D. had received two prior Gardasil vaccinations, her immune system's

[43] The parties do not dispute that B.K.D. first showed symptoms of an illness on October 1, 2011, three days after she received the HPV and FluMist vaccinations. Joint Pre-hearing Submission, filed May 15, 2015, at 1.

[44] Adverse Effects of Vaccines at 51 (Stratton et al., eds. 2012).

[45] The author previously explained, "Antigen exposure initiates an array of reactions involving the immune system, including the activation of white blood cells called *lymphocytes* that fight infection. After antigen exposure, two types of lymphocytes, B cells and T cells, differentiate into effector (e.g. antibody-producing B cells and cytotoxic and helper T cells) and memory cells." Pet'r's Ex. 47 at 1 (emphasis in original).

primary response to the HPV antigens was much faster. Tr. 134. In fact, the IOM study reports, "Due to the development of memory B and T cells during the primary immune response, the latency between subsequent exposure to the antigen and development of the immune response will usually be shorter. The lag phase is generally one to three days." Pet'r's Ex. 47 at 2. Dr. Tornatore opined that because B.K.D. had twice been exposed to the HPV antigens, her immune response to the third vaccination was more immediate, making the latency phase much shorter and causing her to develop symptoms of NMO after three days. Tr. 135.

Dr. Tornatore also cited a study by Tenembaum et al.[46] discussing events preceding ADEM in pediatric patients. See Pet'r's Ex. 25 at 1. The authors of the study reported that the mean latency period between a vaccination and the subsequent development of ADEM was 12.1 days, with a range of two to 30 days. Id. at 2. Additionally, Dr. Tornatore pointed to the Noorbakhsh study's findings that the first symptoms of vaccine-induced ADEM can appear "within days to weeks" after vaccination. Pet'r's Ex. 24 at 1. Similarly, a study of ADEM and MS in children completed by Dale et al.[47] found the average latency period between a demyelinating illness and ADEM symptom onset to be between two to 31 days with a mean latency of 13 days. Pet'r's Ex. 26 at 4. Although the Tenembaum, Noorbakhsh, and Dale articles all referenced ADEM rather than NMO, Dr. Tornatore opined, "the basic concepts in immunology [of ADEM and NMO] are the same, and so I think these [studies] are very applicable to this case." Tr. 136.[48] Dr. Tornatore demonstrated through these articles that B.K.D.'s post-vaccine NMO symptom onset of three days is medically appropriate.

Dr. Tornatore also referenced a study published by the Risk Interval Working Group of the Clinical Immunization Safety Assessment Network ("the Risk Interval Working Group")[49] to support his opinion that B.K.D. could have developed NMO three days after receiving the Gardasil and FluMist vaccinations.[50] The goal of the Risk Interval Working Group's project was to calculate "biologically plausible and evidence-based risk intervals" that could be used by other specialists to perform immunization safety research on ADEM and febrile seizures. Pet'r's Ex.

---

[46] Silvia Tenembaum et al., 59 NEUROLOGY 1224.

[47] R.C. Dale et al., Acute Disseminated Encephalomyelitis, Multiphasic Disseminated Encephalomyelitis and Multiple Sclerosis in Children, 123 BRAIN 2407 (2000) [Pet'r's Ex. 26].

[48] Dr. Tornatore also referenced a second study by Dale et al. regarding the latency period between a vaccination and the symptom onset for NMO. See Pet'r's Ex. 26.

[49] Ali Rowhani-Rahbar et al., Biologically Plausible and Evidence-Based Risk Intervals in Immunization Safety Research, 31 VACCINE 271 (2012) [Pet'r's Ex. 46].

[50] The undersigned notes that the first page of the Risk Interval Working Group's study states the following disclaimer, "The findings and conclusions in this report are those of the authors and do not necessarily represent the official position or views of the CDC." However, as was clarified during the cross-examination of Dr. Leist, one of the Group's individual participants worked in the CDC's immunization office, and each of the Group's members is a well-qualified pediatric and public health specialist. See Tr. 208.

46 at 1-2; Tr. 137-38. The Risk Interval Working Group established primary and secondary risk intervals as follows:

> [T]wo sets of risk intervals to examine the association between vaccines and ADEM would be appropriate. For determining the likelihood of a role of a vaccine in development of neurologic illness in an individual, an interval of [two to] 42 days that remains biologically plausible but is associated with greater uncertainty, was proposed. For epidemiologic assessments of causality between a particular vaccine and ADEM, a primary short interval of [five to] 28 days was proposed. This interval incorporates the time periods best substantiated by available biological and epidemiologic data. A long period of [two to] 42 days could be used as a secondary risk interval.

Pet'r's Ex. 46 at 4; see also Tr. 138.

In summary, Dr. Tornatore testified that NMO could occur three days after vaccination, and he provided medical literature to support his position.

b. Treating Physicians

Dr. Mattson and Dr. Golomb, two of B.K.D.'s treating physicians, also noted a temporal association between B.K.D.'s receipt of the Gardasil and FluMist vaccinations and her onset of NMO. After reviewing B.K.D.'s November 2, 2011 MRI results, Dr. Golomb noted that B.K.D.'s symptoms began shortly after her receipt of the Gardasil and FluMist vaccinations. Pet'r's Ex. 4 at 123. Additionally, after Dr. Mattson confirmed that B.K.D. tested positive for the NMO-IgG antibody, he noted, "[B.K.D.] has had an October 2011 episode, [about] a week after vaccinations, involving numbness and tingling with right leg weakness [] [and] gait deterioration …" Pet'r's Ex. 6 at 13.

2. Respondent's Expert, Dr. Leist

a. Insufficient Period of Time Between Vaccination and NMO

Dr. Leist disagreed with Dr. Tornatore that B.K.D. could have developed NMO three days after receiving the Gardasil and FluMist vaccinations. Dr. Leist described the immune response that invades the central nervous system as a "multistep process" which could not be accomplished in such a short time interval.[51] Tr. 193. He stated, "The time interval of about three days between vaccinations and onset of a cross-reactive cognate immune response is too brief to cause induction or reactivation of a T and plasma cell as well as antibody dependent

[51] Dr. Leist further explained, "[I]n order to have a process within the spinal cord, the immune response needs to be upregulated, there needs to be invasion into the central nervous system, and there needs to be a generation of a … local damage within the central nervous system." Tr. 193.

immune response leading to involvement of the central nervous system." Resp't's Ex. A at 10-11.

Furthermore, Dr. Leist disputed the relevance of some of the medical literature referenced by Dr. Tornatore regarding an appropriate onset, including the Tenembaum article regarding the onset of post-vaccine ADEM. Dr. Leist commented, "Tenembaum et al. reported in the series of 84 children with ADEM that symptoms arose two to 30 (mean 12.1) days after a preceding event in 74 % of the cases. However, their evaluation of the potential causes did not go beyond temporality." Resp't's Ex. A at 11 (referencing Pet'r's Ex. 25 at 1). Also, as mentioned above, Dr. Leist also stated that because B.K.D. did not suffer from ADEM, the Tenembaum study was not applicable to her case. Resp't's Ex. A. at 12.

Additionally, Dr. Leist opined that the study done by the Risk Interval Working Group measuring risk intervals for immunization safety research was insufficient proof of the two to 42 day risk interval. Dr. Leist stated that although the researchers calculated a plausible secondary risk interval of two to 42 days, there was insufficient data to support this position. The Risk Interval Working Group reported:

> Of 250 publications of ADEM reviewed, nine studies met the inclusion criteria, were deemed to be potentially informative, and were assessed in their entirety for any report of ADEM onset following immunization … Only two studies had explicitly indicated the timing of ADEM onset following immunization … The mean onset of ADEM following immunization was 17 days (range [nine to] 30 days).

Pet'r's Ex. 46 at 3. Accordingly, Dr. Leist stated that the results of the Risk Interval Working Group's study actually showed that the potential risk interval of three days was highly implausible, given that there were only two studies that explicitly indicated symptom onset. Finally, Dr. Leist pointed out that the Risk Interval Working Group's study does not reflect the CDC's official position on vaccine risk intervals, despite the fact that an individual CDC employee was part of the research team. Tr. 192-93.

Dr. Leist referenced medical literature by Mannara et al.[52] to support his position that three days is an insufficient time interval within which B.K.D. could have developed NMO after receiving the Gardasil and FluMist vaccinations. In the Mannara study, researchers induced experimental autoimmune encephalomyelitis (EAE) in mice by giving them a vaccine with activated EAE; they then measured the latency period between the vaccination and the onset of EAE symptoms. Resp't's Ex. H at 1. The mice were injected with T cells in order to speed up their immune systems' response. Dr. Leist explained, "Instead of inducing an immune response, you actually give the components of an immune response … to [the] mouse." Tr. 195-96; see also Resp't's Ex. H at 3. The study found that even though the mice had already been exposed to EAE activated T cells, they developed the first neurological symptoms of EAE eight days after injection. Resp't's Ex. H at 3.

[52] Francesco Mannara et al., Passive Experimental Autoimmune Encephalomyelitis in C57BL/6 with MOG: Evidence of Involvement of B Cells, 7 PLOS ONE 1 (2012) [Resp't's Ex. H].

Dr. Leist stated, "This work shows that even when a preformed immune response is present there is a delay in the occurrence of neurologic symptoms." Resp't's Ex. A at 11. Dr. Leist compared B.K.D.'s three day symptom onset with the results from the Mannara study to conclude that the symptoms B.K.D. developed on October 1, 2011, could not have been caused by her Gardasil and FluMist vaccinations. Resp't's Ex. A at 11; Tr. 196.

3. Evaluation of the Evidence

The undersigned finds that the onset of B.K.D.'s NMO occurred on October 1, 2011, when she began complaining of back and abdominal pain. Prior to that date, B.K.D. had no history of NMO or an NMO spectrum disorder, nor had she ever experienced any serious neurological problems. Petitioner has presented preponderant evidence showing that in rare cases, a person's immune response after receiving a vaccination can be as short as three days, especially if the body is already primed with the specific viral antigens.

Dr. Tornatore opined that a three day time frame from vaccination to the onset of NMO symptoms is medically acceptable given the process of molecular mimicry. The medical literature supports Dr. Tornatore's opinion that a person can quickly develop an immune response after a vaccination, especially if there have been previous exposures to the same viral antigens. Tr. 135; see also Pet'r's Ex. 47 at 1; Pet'r's Ex. 25 at 1; Pet'r's Ex. 46 at 1-2. Although the lag phase as discussed in the IOM report was most often reported as between four to seven days or between seven to ten days, Dr. Torantore explained that due to B.K.D.'s previous exposure to the HPV antigens, the immune response after the third round of Gardasil and the FluMist vaccination led to a more brisk autoimmune response. Tr. 135; Pet'r's Ex. 47 at 2. The IOM study reported, "Due to the development of memory B and T cells during the primary immune response, the latency between subsequent exposure to the antigen and development of the immune response will usually be shorter. The lag phase is generally one to three days." Pet'r's Ex. 47 at 2. This brisk immune response was also noted in the development of post-vaccinal ADEM, which can occur anywhere from two to 30 days. Pet'r's Ex. 25 at 2.

Dr. Tornatore's theory that molecular mimicry resulted in B.K.D.'s development of NMO after three days also fits within the second risk interval time frame as established by the Risk Interval Working Group. The Risk Interval Working Group observed that while the primary risk interval for studying adverse reactions to vaccines is approximately five to 28 days, two to 42 days was "biologically plausible" as a secondary risk interval. Pet'r's Ex. 46 at 4. Moreover, while Dr. Leist opined that such intervals are merely suggested for the study of post-vaccinal neurological disorders, the undersigned finds these suggested intervals persuasive. See Tr. 191-92.

Dr. Liest stated that three days was an insufficient time period between vaccination and NMO symptom onset to preponderantly prove a temporal relationship between vaccination and injury in B.K.D.'s case. However, the undersigned notes that Dr. Leist did not sufficiently address Dr. Tornatore's point that B.K.D.'s immune response had been primed by two earlier doses of the Gardasil vaccination. Dr. Liest simply stated that "even in a situation where there

has been a priming occurring by prior exposure, a representation of the same antigen, if we purport that this causes the disease, will still take time … [and] 72 hours … is too short." Tr. 196. Respondent did not adequately address petitioner's argument that the previous receipt of multiple doses of the same viral antigen could speed up the body's immune response.

Moreover, while Dr. Leist cited medical literature in support of his opinion that three days is an insufficient time period by which a person might normally develop NMO in response to a vaccine, the undersigned finds petitioner's evidence more persuasive. Dr. Leist stated that the Mannara study regarding the development of post-viral encephalomyelitis in mice demonstrates that three days is an insufficient time period for a person to develop visible symptoms of NMO after receiving a vaccine. Tr. 195; Resp't's Ex. H at 2. Dr. Leist highlighted the Mannara researchers' findings that mice injected with activated EAE T cells first exhibited motor symptoms of EAE seven days after vaccination to support his opinion that B.K.D. could not have developed NMO from a vaccine after three days. Resp't's Ex. H at 2; Tr. 195-96.

However, Dr. Tornatore pointed out how the Mannara article could be construed to support petitioner's position, because the mice showed non-motor signs of EAE after two days. Resp't's Ex. H at 2. Similarly, B.K.D. showed non-motoric signs of NMO three days after her vaccinations. Tr. 234. Dr. Tornatore argued, "[T]his paper … demonstrates that within two days, you can have evidence of an adverse response from a vaccination." Tr. 234.

Two of B.K.D.'s treating physicians documented a temporal association between the vaccines and the onset of illness. Dr. Golomb, one of B.K.D.'s treating physicians at Riley Hospital, reviewed B.K.D.'s November 2, 2012 MRI results with an ADEM expert and noted in B.K.D.'s file that she received the Gardasil and FluMist vaccinations on Thursday[53] and then experienced "band-like back pain" on Monday. Pet'r's Ex. 4 at 123. Dr. Golomb then mentioned that the vaccine response is typically five to 42 days. Id.

In June 2012, after B.K.D. experienced several recurring episodes of what was thought to be ADEM, she followed up with Dr. Mattson at the MS Center of Indiana University, where it was first postulated that she suffered from NMO.[54] Pet'r's Ex. 6 at 4-5; Pet'r's Ex. 21 at 9-10. On June 12, 2012, B.K.D. tested positive for the NMO-IgG antibody, which her physicians noted as consistent with a diagnosis of NMO. Pet'r's Ex. 6 at 13. Dr. Mattson also reported, "[B.K.D.] has had an October 2011 episode, a week after vaccinations, involving numbness and tingling with right leg weakness [] [and] gait deterioration…" Id. at 4.

The undersigned is persuaded by Dr. Tornatore's argument that B.K.D. could have developed symptoms of NMO three days after receiving the Gardasil and FluMist vaccinations,

[53] The undersigned notes that Dr. Golomb's dates here are incorrect. B.K.D. received the Gardasil and FluMist vaccinations on Wednesday, September 28, 2011, and her symptoms first began on Saturday, October 1, 2011.

[54] B.K.D.'s diagnoses progress from viral/bacterial meningitis to ADEM and then from ADEM to NMO. Both Dr. Tornatore and Dr. Leist agree that B.K.D.'s correct diagnosis from the onset of symptoms on October 1, 2011, is NMO.

and petitioner has demonstrated that this three day time frame is medically appropriate. Therefore, petitioner has satisfied her burden of presenting preponderant evidence of Althen Prong Three.

IV. Conclusion

For the reasons discussed above, the undersigned finds that the petitioner is entitled to compensation because she has provided sufficient evidence that preponderates in her favor. A separate damages order will issue.

IT IS SO ORDERED.

/s/ Nora Beth Dorsey
Nora Beth Dorsey
Chief Special Master